Behavioural Brain Research 274 (2014) 291–301

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

Mechanisms underlying sleep–wake disturbances in alcoholism: Focus on the cholinergic pedunculopontine tegmentum

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HIGHLIGHTS

- The cholinergic pedunculopontine tegmentum (CCC-PPT) regulates sleep–wake activity.
- Both REM sleep and wakefulness are regulated by the CCC-PPT.
- CCC-PPT $GABA_B$, NMDA, and kainate receptors are involved in sleep–wake regulation.
- Sensitivity of these receptors in the brain is altered by chronic alcohol use.
- Such alterations in the CCC-PPT may lead to alcohol-induced sleep disruption.

ARTICLE INFO

Article history:
Received 9 May 2014
Received in revised form 11 August 2014
Accepted 13 August 2014
Available online 20 August 2014

Keywords:
Alcohol addiction
Glutamate
GABA
Pedunculopontine tegmentum
Receptor
Sleep–wakefulness

ABSTRACT

Sleep–wake (S–W) disturbances are frequently associated with alcohol use disorders (AUD), occurring during periods of active drinking, withdrawal, and abstinence. These S–W disturbances can persist after months or even years of abstinence, suggesting that chronic alcohol consumption may have enduring negative effects on both homeostatic and circadian sleep processes. It is now generally accepted that S–W disturbances in alcohol-dependent individuals are a significant cause of relapse in drinking. Although significant progress has been made in identifying the socio-economic burden and health risks of alcohol addiction, the underlying neurobiological mechanisms that lead to S–W disorders in AUD are poorly understood. Marked progress has been made in understanding the basic neurobiological mechanisms of how different sleep stages are normally regulated. This review article in seeking to explain the neurobiological mechanisms underlying S–W disturbances associated with AUD, describes an evidence-based, easily testable, novel hypothesis that chronic alcohol consumption induces neuroadaptive changes in the cholinergic cell compartment of the pedunculopontine tegmentum (CCC-PPT). These changes include increases in *N*-methyl-D-aspartate (NMDA) and kainate receptor sensitivity and a decrease in gamma-aminobutyric acid ($GABA_B$)-receptor sensitivity in the CCC-PPT. Together these changes are the primary pathophysiological mechanisms that underlie S–W disturbances in AUD. This review is targeted for both basic neuroscientists in alcohol addiction research and clinicians who are in search of new and more effective therapeutic interventions to treat and/or eliminate sleep disorders associated with AUD.

Contents

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http://dx.doi.org/10.1016/j.bbr.2014.08.029
0166-4328/

1. Introduction

Moderate to severe alcohol use disorders (AUD) are chronic relapsing conditions that are progressive and have serious detrimental health outcomes. The development of AUD is characterized by frequent episodes of intoxication, preoccupation with alcohol, use of alcohol despite adverse consequences, compulsion to seek and consume alcohol, loss of control in limiting alcohol intake, and emergence of a negative emotional state in the absence of the drug [1]. Excessive alcohol use is a major contributor to the burden of disease and a host of injuries (related to vehicular, industrial, and many other accidents) in the United States and many other developed and developing countries. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), more than 18 million people in the United States either abuse or are dependent on alcohol [2], with an annual cost to of approximately $235 billion, out of which more than $23.5 billion could be attributed to insomnia and other sleep disorders. Thus, the consequences of sleep problems in alcoholics are economically and clinically significant. AUD is now considered a neurobiological illness in which chronic high dose alcohol consumption leads to alcohol-induced neuroplastic changes in the normal neuronal circuitry involved in the regulation of adaptive behaviors(most notably reward related behaviors). During the last 50 years, a vast amount of clinical literature, as well as both basic human and animal research, has shown that alcohol has a profound impact on sleep and circadian rhythm [3–6]. Although significant progress has been made toward understanding the neurobiology of alcoholism [7–11] and the neurobiology of sleep [12–14], the neurobiological underpinnings that underlie the sleep–wake (S–W) disturbances associated with alcohol abuse and alcohol withdrawal have not yet been clearly identified.

This review first describes the S–W stages in both human and other laboratory animals that are used to understand the mechanisms and functions of sleep. It then briefly summarizes alcohol's effects on S–W activity of non-alcoholics and alcoholics during active drinking and during withdrawal. Finally, based on the existing literature concerning the neurobiological mechanisms of sleep regulation and alcohol's effects on our brain, it describes possible neurobiological mechanisms underlying S–W disturbances in alcoholism.

2. Sleep stages in human and other mammals

Sleep in mammals is not a homogenous behavioral state, but rather is a continuum of mixed states that differ in their physiology, chemistry, and phenomenological experiences [12,13]. Because some human sleep stages are named differently from those in animals, and since the present description on the possible neurobiological mechanisms of AUD is based on animal research, the following text describes the similarities and differences between human sleep stages and those of animals.

Human Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep alternate throughout each of the four to six sleep cycles that occur every night. The most common and preferred animal models used in sleep research include the mouse, rat, and cat; in these animals, NREM-REM sleep cycles are much shorter than in human and non-human primates [12]. This cyclic NREM-REM sleeps epochs in rodents and cats continue throughout the day and night, except when the animal is engaged in activities that require wakefulness. In humans, NREM sleep is further subdivided into four stages (I, II, III, and IV), each corresponding to an increasing depth of sleep [12,13]. NREM stage one (NREM-I) sleep is characterized by relatively low-amplitude (<50 μV) theta frequency activity (4–7 cycles per second) (Hz) and vertex sharp waves in the EEG. Stage two (NREM-II) sleep is characterized by the appearance of distinctive sleep spindles (lasting between 0.5–1.0 s and peak amplitudes of 100 μV) composed of augmenting and decrementing waves at a frequency of 12–14 Hz and K-complex (a negative sharp wave followed immediately by a slower positive component) waveforms in the EEG. Stage three (NREM-III) sleep is characterized by the addition of high-amplitude (>100 μV) slow waves (1–4 Hz), with no more than 50% of the EEG record occupied by the slow waves. In stage four (NREM-IV), the EEG record is dominated by high-amplitude (150–250 μV) slow waves (1–4 Hz). Throughout this process, as the EEG frequency is decreasing and the amplitude is increasing, muscle tone progressively declines and may be lost altogether in most of the somatic musculature. Slow rolling eye movements first replace rapid saccadic eye movements of waking and then subside, with the eyes finally assuming a divergent upward gaze. The deepest stages of NREM sleep, III and IV, are collectively called slow wave sleep (SWS; also known as delta sleep). Distinctions between stages of NREM sleep in animal models differ slightly from those in humans. In the aforementioned animals, NREM sleep is normally subdivided into two stages (SWS-I and SWS-II). SWS-I is identified by the presence of sleep spindles in the cortical EEG. SWS-II is considered deep sleep and is identified by the presence of high-amplitude, low frequency waves in the cortical EEG (delta sleep). Human NREM stages I and II sleep are comparable to mouse, rat, and cat SWS-I, whereas stages III and IV NREM sleep in humans are comparable to the animal SWS-II [12,13].

After varying amounts of time (depending upon the size of the animal and its brain), this progressive set of changes in the EEG reverses itself and the EEG eventually resumes the low-amplitude, fast character previously seen in waking [12]. Instead of waking, however, behavioral sleep persists. Muscle tone, which was first passively decreased during NREM sleep, is now actively inhibited. Stereotyped bursts of saccadic eye movements, called rapid eye movements (REMs), appear in the electrooculogram (EOG) and give this state the name REM sleep [12]. This phase of sleep has also been called activated sleep (due to increased EEG activation) and paradoxical sleep (to signal the maintenance of increased behavioral arousal threshold in the presence of the activated brain). Supplemental to these polysomnographic signs, other REM sleep-specific physiological signs are: myoclonic twitches in the facial, digital, and even major proximal skeletal muscles, pronounced fluctuations in cardio-respiratory rhythms, and core body temperature and penile erection in males and clitoral engorgement in females. Physiological signs of REM sleep in humans are, for the most part, comparable to physiological signs of REM sleep in the rat and cat. However, another sleep stage, one between SWS-II and REM sleep, has been identified mainly in rats and cats and is called the transitional sleep stage (tS-R) [12,15]. During this transitional stage, the appearance

of cortical EEG signs is similar to the cortical EEG of SWS-I and hippocampal and pontine EEG signs are similar in appearance to those during REM sleep, but with less intensity. Since most animal sleep studies have not recorded hippocampal and/or pontine EEG, such studies have often considered this stage to be SWS-I. Similarly, in sleep studies of healthy humans, hippocampal and/or pontine EEG cannot be recorded to help identify sleep stages. Therefore, based on EEG signs in humans, this transitional sleep stage has always been identified as Stage II NREM sleep [15].

3. Effects of alcohol consumption on sleep–wake disturbances in non-alcoholics

In healthy non-alcoholics, acute consumption of alcohol 1–3 h before bedtime decreases sleep latency, increases NREM sleep stages III and IV (also known as SWS), increases EEG power density in the delta frequencies (0.3–4 Hz), and decreases REM sleep during the first half of nocturnal sleep time [5,6,10,16–23]. However, during the second half of nocturnal sleep time, wakefulness (W) and REM sleep increase resulting in severe disturbances in sleep architecture. Unlike alcohol consumption closer to bedtime, consumption of alcohol in the late afternoon (6 h before scheduled bedtime) decreases sleep efficiency (i.e. continuous sleep), total sleep time, and REM sleep [24]. Consistent with human studies, animal studies performed in rodents have shown that acute treatment of alcohol reduces time of sleep onset (latency to sleep), increases SWS, and decreases REM sleep for about 3–6 h, after which there are increases in W and rebound REM sleep [25–30].

4. Effects of alcohol on sleep–wake disturbances in AUD

Several studies have investigated the effects of continued alcohol consumption in AUD individuals [3,5,6,31–33]. These studies have shown that alcohol consumption in AUD individuals: increases sleep latency; decreases total sleep time; increases NREM sleep (which then returns to baseline levels during withdrawal); and suppresses REM sleep (which then either rebounds or returns to baseline levels during withdrawal). Additionally, on withdrawal nights, sleep latency increases and total sleep decreases, suggesting that alcoholic patients develop tolerance to the sleep-inducing effects of alcohol [20,34]. Studies have also shown that chronic alcohol consumption increases daytime sleepiness and reduces daytime alertness, indicating that chronic alcohol use not only decreases total amounts of sleep but also alters normal circadian patterns of sleep pressure [35]. It has also been indicated that AUD individuals are susceptible to virtually every type of sleep problem [4,6]. As in human studies, animal studies have shown that 6 weeks of chronic exposure to alcohol in water or in a liquid diet increases W and reduces both SWS and REM sleep during the light period, but decreases W and increases SWS during the dark period [36,37]. Animal studies have also shown that continued alcohol consumption causes alterations in the circadian distribution of S–W stages [29,36–38].

5. Effects of alcohol withdrawal on sleep–wake disturbances in AUD

The most severe consequences of alcohol withdrawal appear during the initial week of abstinence, but protracted withdrawal symptoms may persist as long as 2 years [22,39–48]. During alcohol withdrawal, sleep efficiency continues to be reduced. Also, there are increases in sleep latency, W, and REM sleep, and a decrease in NREM sleep [3,43,48–54]. Hallucinations of delirium tremens, a severe manifestation of alcohol withdrawal, represent an intrusion of REM sleep processes into the waking state [55], which is another indication of increased REM sleep pressure during alcohol withdrawal. In addition, alcohol withdrawal can also intensify other sleep disorders such as sleep apnea and periodic limb movements [49,50,56,57]. In healthy people, the majority of REM sleep occurs during the last third of the night, but in alcoholics that have been abstinent for 10–30 days, the majority of REM sleep occurs during the first two-thirds of the night, suggesting an abnormal phase advance in REM sleep [46]. Thus, early stages of withdrawal also produce alterations in the circadian pattern of REM sleep, which will often persist even during prolonged recovery from drinking [3,43,48,49,57]. Disrupted sleep patterns, especially both increased REM sleep pressure during early abstinence and continued insomnia, are predictive of relapse into drinking behavior [40,43,51,53,58–60]. There is evidence that some AUD individuals may resume drinking in an attempt to self-medicate their sleep problems [3]. Similar to human studies, animal studies performed in rodents suggest that insomnia-like symptoms, which include increases in W and REM sleep and reductions in total sleep time and delta activity, are observed during withdrawal in alcohol-dependent rats [29,36,37,61–65].

6. Alterations in EEG activity in healthy adults and adults with AUD

For the quantification of baseline EEG activity changes, brain waves are typically divided into the following frequency bands: delta (0.1–3.5 Hz), theta (3.5–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), beta (16–32 Hz), and gamma (32–80 Hz). Some of these wave bands are again further divided arbitrarily as “fast” and “slow” (e.g. slow alpha: 8–10 Hz; fast alpha: 10–12 Hz; slow beta: 16–20 Hz; fast beta: 20–32 Hz). A number of studies have shown that the decreases in the predominant baseline frequency and increases in power spectrum are the most common effects of ethanol ingestion on the baseline EEG activity in healthy adults [66–72]. Low doses of alcohol ingestion, which cause behavioral arousal and euphoria, decrease mean amplitude of EEG and increase theta and alpha band activity [68,70,72,73]. Higher doses of ingested alcohol produce depression of activity; decrease frequency and increase mean voltage in all frequency bands [74,75]. Reports of ethanol-induced changes in beta activity are somewhat contradictory. For example, some have reported decreased beta power with subsequent replacement by alpha activity [67,73,76], increased beta activity [68,76], both increases and decreases in mean frequency in the beta range [77], and no ethanol-induced effects on beta [78–80]. The baseline EEG activity pattern, even without ingestion of alcohol, can also be used as a physiological marker for the identification of individuals with predisposition of later alcoholism. A comparison of the baseline EEG activity of light and moderate drinkers who were negative for a family history of alcoholism showed that moderate drinkers exhibited greater spectral power and higher peak frequency in the beta band [73,81]. EEGs in men with a positive family history of alcoholism show more fast alpha frequency activity than matched controls with negative family history [81,82]. It is also shown that alcohol consumption elicited different EEG patterns, with greater increases in slow alpha activity, in men at high risk for development of alcoholism [81,82]. High-intake binge drinkers exhibit higher spectral power than the non- and low-intake binge drinkers in the delta and fast beta (20–32 Hz) bands [83]. As in human subjects, ethanol-preferring (i.e. P strain) rats exhibit greater delta frequency activity and lower-peak theta frequency than the ethanol non-preferring (NP) line of rats [84,85]. High-alcohol drinking (HAD) rats also exhibit greater spectral power for the delta and theta bands and higher activity in the fast beta (13–32 Hz) and fast alpha (9–12 Hz) bands compared to low-alcohol drinking (LAD) rats [86]. Alterations in resting EEG

activity have also been described in the alcoholic patients [87–93]. Adults with AUD manifest less prevalent and lower alpha power and more prevalent and higher beta power than do those without AUD [89,91,94,95]. It has also been shown that individuals with AUD exhibit higher theta power and lower delta power than do matched non-AUD controls [96–98]. In summary, the majority of baseline EEG activity investigations demonstrated that the mean power of EEG activity decreases in delta and alpha bands and increases in beta band in both individuals with AUD and in young adults at risk for the future development of AUD.

Some studies have also examined the acute effects of ethanol ingestion on the EEG gamma band activity rhythm. One EEG activity recording study in healthy social drinkers has reported that ingestion of 0.5 and 0.75 g/kg doses of alcohol suppressed auditory transient evoked gamma band (40-Hz) oscillatory response [99]. Another study, using magnetoencephalography (MEG) has shown that ingestion of 0.8 g/kg dose of alcohol increased peak amplitude and decreased peak frequency of visual grating and finger abduction paradigms-induced gamma band EEG activity [100]. Interestingly, it has also been reported that the early evoked gamma band response in the frontal and parietal regions during target stimulus processing is significantly less in male adolescent subjects, with a high risk for alcoholism, compared to normal control subjects [101]. This finding suggests that the deficient early-evoked gamma band response may precede the development of AUD and could be a potential endophenotypic marker of AUD risk. High density EEG activity recording studies have shown that with either compared with non-AUD subjects or light drinkers, heavy drinkers and drinkers with more severe AUD exhibit increased synchronization in the gamma band, a sign of an abnormal changes in hippocampal–neocortical connectivity in heavy drinkers and a sign of a premature form of ageing in those with more severe AUD [102–104]. In summary, the mean powers of EEG activity decreases in delta and alpha bands and increases in beta and gamma bands in heavy drinkers, young adults predisposed with the future development of alcoholism, and AUD.

The findings described above regarding changes in EEG activity associated with the chronic excessive alcohol consumption of alcohol may provide a basis for identification of novel interventions for the treatment of AUD. They suggest to us that drugs that can produce a shift in the EEG activity pattern by decreasing high-frequency beta band and increasing low-frequency alpha band, perhaps, also increase evoked gamma band activity may be good candidate medications for testing in future AUD treatment clinical investigations. Consideration should also be given to the possibility that drugs that have specific effects on EEG activity, such as increasing alpha-band activity can be targeted to treat AUD individuals who display a particular EEG pattern such as decreased alpha activity.

7. Use of animal models to study alcoholism

One of the challenges in designing pre-clinical studies of the effects of ethanol consumption on sleep is the selection of the appropriate animal model of chronic alcohol exposure. A major problem that investigators confront is that outbred strains of rats will not, under normal circumstances, voluntarily consume alcohol in sufficient amounts to produce levels of intoxication that can be considered to be equivalent to those seen in humans with alcohol use disorders and which produce reliable states of alcohol dependence. To address this problem several models of chronic alcohol exposure have been developed in rodents (i.e. rats and mice) that lead to sustained blood alcohol concentrations that are in the range of those observed in individuals with AUD. Models used in sleep studies, thus far, include the delivery of alcohol using intragastric intubation, as a vapor, or via ethanol-containing liquid diets.

The administration of alcohol by intragastric administration has been used successfully in several studies to examine the effects of alcohol administration on S–W activity in the rat [29,30,38,104–106]. The intragastric procedure can produce dependence in periods as short as 4 days [107]. High doses of ethanol, when administered intragastrically, can produce marked signs and symptoms of withdrawal including convulsive seizures [108,109]. The use of the intragastric intubation for the delivery of alcohol has clearly been demonstrated to produce disruptions in S–W activity in the rat and mouse, which have similarities to alcohol-induced changes in this activity that are seen in individuals with alcohol use disorders [28,38,63,104–106]. This procedure, however, lacks face validity as a model of alcoholism in that it involves the passive delivery of single large boluses of alcohol administered over a relatively short time interval, i.e. a few days. Of major concern is that very large doses of ethanol may produce toxic insults to the brain that may not occur in animals that self-regulate their intake of alcohol. Also, a single bolus of ethanol may not interact with the mechanisms that regulate sleep in a manner similar to that, which would be observed when ethanol intake fluctuates repeatedly throughout the day with intermittent ingestion of alcohol only during periods of wakefulness. A final concern is that the intragastric administration of alcohol using gastric intubation is in itself a highly stressful procedure that may produce behavioral and other effects that may not be seen when ethanol is administered under less stressful conditions.

Another method that has been employed by a few investigators in studies of the effects of ethanol on sleep is the use of a liquid diet as a vehicle for the delivery of alcohol [29,36,37]. The repeated ingestion of liquid diet containing 10% ethanol may lead to blood alcohol concentrations of more than 200 mg/dl [110]. The amount of ethanol consumed by animals given access to ethanol liquid can be large enough to produce signs of withdrawal after the discontinuation of access [110,111]. Use of the ethanol liquid diets allows for the consumption of alcohol over extended periods of time, i.e. over many weeks, and animals self-regulate their intake of alcohol allowing this to occur with the daily fluctuations of S–W activity. Consequently, patterns of ethanol intake may have similarities to those seen in AUD. Animals, however, are essentially forced to consume alcohol and, consequently, the face validity of the liquid ethanol diet procedure as a model of human alcohol use disorders must be considered to be limited. In our ongoing studies of the neurobiological mechanisms underlying alcohol dependence in the rat model, ethanol is delivered in 9% concentration in a liquid diet. The results of this ongoing research showed that this experimental method was very effective in inducing a sleep phenotype of alcohol dependence and alcohol withdrawal (Fig. 1). A number of studies in the rat model have indicated that 9% ethanol in liquid diet delivers approximately 10–16 g/kg of ethanol per day with an average blood concentration in the range of 120–400 mg/dl [29,111–113]. It has also been shown that a 9.0% (v/v) ethanol liquid diet produces sufficient dependence to enhance levels of responding for ethanol during periods of withdrawal [114]. Acoustic startle response, a measure of excitability, remains elevated above control for at least 72 h after discontinuation of an 8.7% liquid ethanol diet. Changes in daily distributions of SWS and REM sleep were seen in rats given a 6% liquid ethanol diet over periods of 3–6 weeks [29,37].

Alcohol dependence can also be produced in animals by exposing them to ethanol vapors [115]. This procedure allows for the continuous delivery of ethanol in doses high enough to allow alcohol blood concentrations to reach the range of between 150 and 200 mg/dl. Delivery of ethanol in vapor form does not stress animals to which gastric intubation may and allows for ethanol to be administered on chronic basis. Several groups of investigators have

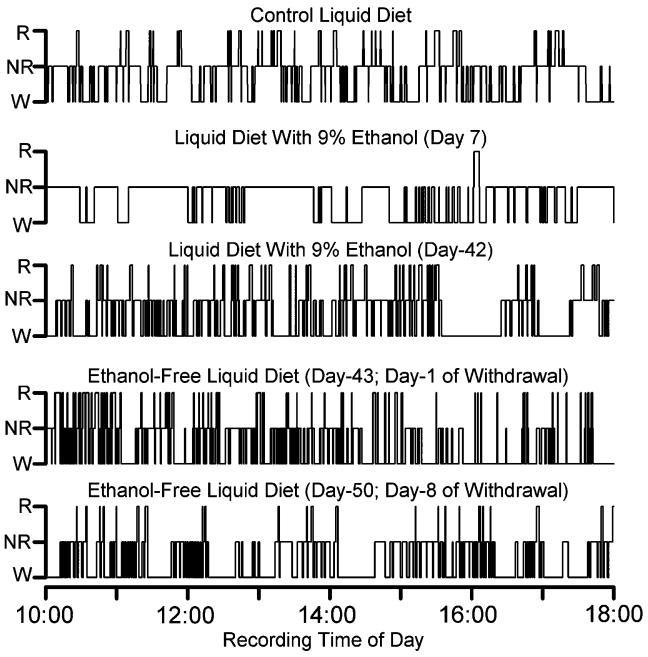

Fig. 1. Typical example of the progression of sleep–wake architecture that occurs in rats over the course of 6 weeks of chronic alcohol consumption followed by 8 days of alcohol abstinence. The dose of ethanol in the liquid diet was increased gradually during the first 5 days: 3% ethanol on the first 2 days, 6% ethanol on the third and fourth days, then 9% ethanol (full dose) from the fifth day until the end of the 6-week period. Control animals received an ethanol-free liquid diet of equal caloric content (adjusted with dextrose). Then, from the beginning of the seventh week to the end of eighth week both groups of rats received an ethanol-free liquid diet with a caloric content identical to that of the liquid diet consumed during the previous 6-week period. These continuous step hypnograms plot occurrence and duration of polygraphically and behaviorally defined wakefulness (W), non-REM sleep (NR; i.e. SWS), and REM sleep (R). Note that at the beginning of alcohol consumption, W and R decreased while NR increased. However, after a long period of continual alcohol consumption (6 weeks), W and R pressure increased while NR decreased. Then, during the initial period of withdrawal (Day-1), W and R pressure further increased while NR further decreased. Also, phase advance of R is clearly evident in both the final day of alcohol consumption and the first day of withdrawal. Finally, after 8 days of withdrawal, the S–W architecture of alcohol consuming rats began to resemble that of the control liquid diet-consuming animals.

used the ethanol vapor procedure to examine the effects of chronic ethanol exposure on sleep related EEG activity during withdrawal in rodents [61,116,117]. In mice exposed to ethanol changes in sleep architecture including reduced non-REM sleep and increased REM sleep corresponded to those seen in humans during withdrawal [116]. The limitations of the ethanol exposure procedure are that animals do not regulate their own intake of alcohol and that continuous exposure to alcohol vapors would not be expected to have fluctuations in blood alcohol concentration that are related to patterns of S–W activity. Another major limitation of this method is that it negatively affects the physiology of the respiratory system.

Several methods of chronic alcohol self-administration have been developed that have not yet been used to study the effects of alcohol on S–W activity. These include intra-gastric ethanol self-infusion [118], intermittent access to high dose ethanol [119], and ethanol self-administration by strains of alcohol-preferring rats [120]. All of these procedures can produce blood alcohol concentrations that are seen in individuals with AUD. They all offer the advantage of animals controlling their own intake of alcohol. As such they offer the opportunity to study the effects of alcohol on sleep using models of AUD with improved face validity in which alcohol concentrations vary in synchrony with animals' S–W cycles.

8. Possible mechanisms of alcohol's action in producing sleep–wake disturbances

Since the neurobiological mechanisms underlying alcohol's effects on S–W behavior remain poorly understood, our tentative explanation of these mechanisms will rely heavily on the well-known neurobiological mechanisms of S–W regulation and neurobiology of alcohol addiction. There are some excellent reviews on the basic neurobiology of S–W behavior and neurobiology of alcohol addiction [7–12,14,121].

8.1. In non-alcoholics

It is already known that γ-aminobutyric acid (GABA) and glutamate receptors are the major targets for ethanol, and, more specifically, that ethanol activates GABA receptors and inactivates several glutamate receptors including L-α-amino-3-hydroxy-5-methyl-isoxazole-4-proprionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors [122–127]. Ethanol also increases the activity of GABA receptors by facilitating the release of GABA and by elevating levels of neuroactive steroids that act to positively modulate $GABA_A$ receptor systems [128,129]. Also, both GABA and glutamate receptors are involved in the regulation of S–W states [12,13,81,130–138], specifically: (a) increased release of GABA from the preoptic-hypothalamic areas (POA) activates GABA receptors (mainly $GABA_A$-type) on the neurons in the W-promoting areas of the brain that ultimately induce SWS (for details of this mechanism, see [12]); (b) activation of $GABA_B$ receptors on pedunculopontine tegmental (PPT) cholinergic cells suppresses neuronal activity, which in turn suppresses both REM sleep and W [135,138]; (c) inhibition of NMDA-type glutamate receptors on PPT cholinergic cells suppresses W and inhibition of kainate-type receptors suppresses REM sleep [130–133]. Therefore, it is logical to suggest that the primary causal mechanisms of acute alcohol consumption-induced increased SWS could be the inhibition of W-promoting neurons via activation of $GABA_A$ receptors, whereas decreased REM sleep could be caused by the activation of $GABA_B$ receptors and/or inhibition of kainate-type of glutamate receptors on PPT cholinergic cells. It has been recently shown that ethanol treatment increases extracellular levels of adenosine [38], which is a metabolite known to participate in the $GABA_A$ receptor activation-mediated induction of SWS, via activation of neurons in the W-promoting areas of the brain [12]. Therefore, it is likely that the SWS-increasing effect of alcohol may be caused by both $GABA_A$ and adenosine receptor activation-mediated inhibition of cells in the W-promoting areas of the brain [12].

8.2. In actively drinking and abstinent alcohol-dependent individuals

A large number of studies on the neurobiology of alcoholism have provided evidence to show that chronic exposure to high alcohol doses during the transition from non-harmful alcohol use to AUD induces adaptive changes in neural circuits that control motivational processes, including arousal, reward, and stress [9,123]. These neuroadaptations produce changes in sensitivity to alcohol's effects following repeated exposure (i.e. sensitization and tolerance) and during a withdrawal state following discontinuation of alcohol use [9,123,139,140]. Alcohol interacts with many neurotransmitters and neuromodulators (e.g. dopamine, DA; serotonin, 5-HT; norepinephrine, NE; acetylcholine, Ach; GABA; glutamate; adenosine; opioid; orexin; ghrelin; corticotrophin-releasing factor, CRF; and neuropeptide Y) in the brain's reward and stress circuits to produce its positive and negative reinforcing effects. These interactions also can lead over time to neuroadaptations to alcohol-induced changes in neuronal function [9,10,122,123,140–152]. In

alcoholism, neuroadaptation means that in response to chronic exposure to alcohol, the brain adjusts neuronal activity to compensate for alcohol's effects on neuronal functioning to maintain its "normal" activity levels. Major features of neuroadaptation to chronic alcohol consumption include decreased inhibitory response of $GABA_A$ receptor systems [153,154] and hyperactivity of excitatory glutamate receptor (i.e. AMPA, NMDA, and kainate) systems [3,5,6,9,122,123,140,142,155]. There is also evidence of diminished responsiveness of pre-synaptic $GABA_B$ receptors to its agonist, baclofen, in the hippocampus during withdrawal from alcohol [156]. With chronic ethanol administration, tolerance may develop to ethanol-induced elevation of neuroactive steroids [157].

Ethanol-induced functional changes in AMPA, $GABA_A$, and NMDA receptor systems may be related, in part, to changes in the levels of expression of specific receptor subunits in select brain regions, including the amygdala, cerebral cortex, and hippocampus, which is of importance because the subunit composition of these receptors determines their propensity towards either hyperexcitability or inhibition of excitability as well as their sensitivity to alcohol and other sedative agents [153,158]. When alcohol is discontinued, these alterations may persist, at least for a while, resulting in increased arousal that manifests as withdrawal symptoms, including S–W disruptions.

Interestingly, one of the major brain areas in the S–W regulating network that actively regulates both W and REM sleep is the cholinergic cell compartment of the PPT (CCC-PPT) [12,13,136,159]. For example, neuropharmacological and physiological studies have shown that glutamatergic activation of kainate receptors on PPT cholinergic cells induces REM sleep by raising neuronal activity to a medium level, whereas glutamatergic activation of NMDA receptors on these same PPT cholinergic cells induces W by increasing neuronal activity to its highest level [12,130–133,159,160]. On the other hand, GABAergic activation of $GABA_B$ receptors inhibits these PPT cholinergic cells, which in turn suppresses both REM sleep and W and increases SWS [135,138]. If the neuroadaptation theory is also applicable for the PPT (discussed above), then it is likely that the PPT of AUD individuals will exhibit reduced sensitivity to $GABA_B$ receptor activation, which could potentially increase W and REM sleep and decrease SWS [13,135,139]. Based on this neuroadaptation theory, it is also likely that the PPT of AUD individuals will have increased sensitivity of kainate and NMDA receptors. Again, this type of neurochemical condition in the PPT is ideal for increasing W and REM sleep and suppressing SWS [12,130–133,159,160]. In support of this suggestion, one pharmacological study on human subjects has shown that decreased SWS and increased REM sleep pressure after alcohol withdrawal is caused by the increased sensitivity of cholinergic system [161]. Based on this evidence, we suggest that the CCC-PPT is one of the major targets of alcohol-associated neuroadaptation, which ultimately causes S–W disturbances, but this hypothesis has not yet been examined.

The suprachiasmatic nucleus (SCN) is critical in synchronizing circadian rhythms and these rhythms can be observed in outputs such as the patterning of the S–W cycle, core body temperature, and secretion of endogenous hormones [162–168]. Based on a vast amount of anatomical, physiological, pharmacological, and molecular evidence, it has been suggested that the PPT and basal forebrain (BF) cholinergic inputs to the SCN are crucial for maintaining normal circadian rhythm, and over-activation of these cholinergic systems could result in phase advance of circadian rhythms [162,164,169,170]. In alcohol-dependent individuals, one of the major signs of S–W circadian disturbances is the abnormal phase advance in REM sleep. It is already known that the majority of BF cholinergic cells are involved in the induction of W while the other cells are involved in the induction of SWS, but both of these cell groups suppress REM sleep [12,171,172]. On the other hand, activation of PPT cholinergic cells increases REM sleep [136]. Therefore, in alcohol-dependent individuals, phase advance in REM sleep could potentially be caused by the over-activation of cholinergic cells in the PPT (but not in the BF).

As discussed above, research on alcohol and sleep has suggested that REM sleep pressure is predictive of relapse into alcohol drinking. Interestingly, research in drug addiction has demonstrated that the primary mechanism for relapse (i.e. reinstatement of drug-seeking behavior, an animal model of relapse) involves activation of glutamatergic cells in the medial prefrontal cortex (mPFC), which then activates dopaminergic (DAergic) projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) [173–179]. Additionally, a number of anatomical, behavioral, physiological, and pharmacological studies have provided evidence to demonstrate that the CCC-PPT receives excitatory input from the mPFC [179–182] and sends cholinergic afferent projections to the VTA [183–186], where they synapse on DAergic neurons that then project to the NAc [180,181,187–195], resulting in the release of DA in the NAc [183,196–198]. Furthermore, administration of a partial nicotinic receptor agonist varenicline has been shown in both preclinical and clinical trials to reduce ethanol consumption [199–202]. Given the role of the VTA in mediating the rewarding effects of ethanol and in reward prediction, it is plausible that the PPT, via its anatomical connection with this structure, may play an important role in the reinstatement of alcohol-seeking behavior, but this hypothesis has not yet been examined.

Orexin/hypocretin, NE, and CRF are also known to modulate W behavior [12] and they act in concert in the extended amygdala to modulate stress-related components of addiction [7–9,148] and might be involved in the promotion of W in AUD S–W disorders, but this has not yet been supported by empirical evidence. Also, there is no evidence linking increased Orexin/hypocretin, NE, or CRF neurotransmitters to the enhancement of REM sleep amount or pressure. Another neurotransmitter, 5-HT, is also known to participate in the regulation of the S–W cycle [12]. There is a well-established link between 5-HT depletion, impulsivity, and alcohol-drinking behavior in rats and humans [146,203–205]. During alcohol withdrawal, 5-HT release in the NAc of rats is suppressed, and this reduction is partially reversed by self-administration of alcohol during withdrawal [206]. It is also known that this decreased 5-HT activity favors cholinergic activation-mediated REM sleep induction [12]. Therefore, changes in the 5-HT system may also participate in the PPT cholinergic system-mediated S–W disturbances in abstinent alcoholics. However, some other studies have suggested that 5-HT may in fact not be involved in the S–W disturbances in AUD individuals [3,5,6].

Our working conceptual model is designed to illustrate only the possible mechanisms of S–W disturbances in alcohol addiction, focusing only on the role of the PPT in the development of sleep disorders that result from chronic exposure to ethanol (Fig. 2). Given the known anatomical connections between the PPT and the VTA, it seems reasonable that changes in PPT activity might influence drug relapse via this structure. This is clearly suggested by the finding that lesioning of the PPT blocks the expression of ethanol-induced reward, as measured by place preference, only in dependent withdrawn mice [207]. In addition to its role in mediating the rewarding effects of ethanol, the VTA is also implicated in mediating the prediction of the availability of rewards (via phasic firing of dopaminergic neurons) [208,209] and signals for aversive stimuli [210]. Collectively, this evidence suggests that the PPT may act via the VTA to influence alcohol consumption and seeking behaviors. Thus, the neuroadaptation at the level of CCC-PPT may be critical patho-physiological mechanism for the S–W disturbances in AUD.

The hypothesis that S–W disturbances in AUD may be caused by the neuroadaptation at the level of CCC-PPT (hypersensitivity

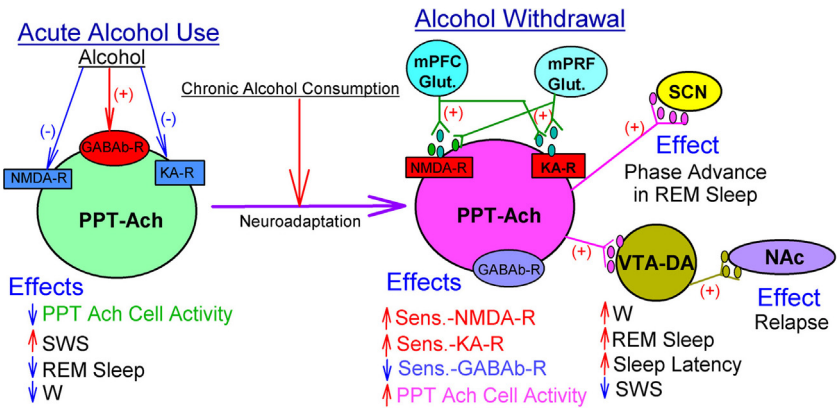

Fig. 2. A working model of the mechanisms underlying sleep–wake disturbances in chronic alcohol consumption. This model illustrates the neurobiological mechanisms underlying the effects of alcohol on sleep–wake disturbances. The text for this model is discussed above. Abbreviations: NMDA-R, NMDA receptor; GABAb-R, GABA-B receptor; KA-R, kainate receptor; PPT-Ach, pedunculo-pontine tegmental cholinergic cell; SWS, slow-wave sleep; REM sleep, rapid eye movement sleep; W, wakefulness; mPFC, medial prefrontal cortex; mPRF, medial pontine reticular formation; Glut., glutamatergic cells; SCN, suprachiasmatic nucleus; VTA-DA, ventral tegmental area dopaminergic cell; NAc, nucleus acumbens; Sens., sensitivity; (+), activation; (−), inhibition; ↑, increase; ↓, decrease.

of kainite and NMDA receptors) is also supported by the findings that gamma band activity increases in AUD [102,103]. For example, all cells in the CCC-PPT are geared to fire at gamma band frequencies and the generation of this activity involves voltage-dependent high threshold N- and P/Q-type calcium channels (reviewed in [211–214]). It has been suggested that this CCC-PPT-mediated gamma band activity generation during REM sleep involves kainate receptor mediated activation of intracellular protein kinase A (PKA) and during wakefulness it involves NMDA receptor activation-mediated activation of intracellular CaMKII (reviewed in [211,212]). Therefore, the increased gamma band activity in AUD is likely to be due to increased kainate and NMDA receptor sensitivity in the CCC-PPT.

9. Concluding remarks

The CCC-PPT plays a key role in regulating both W and REM sleep. Many of the receptor systems, including the NMDA, kainate, and $GABA_B$ systems whose activity is altered by the administration of ethanol have been implicated the regulation of W and REM sleep by the CCC-PPT. Given the evidence that chronic exposure to ethanol may enhance the excitability of NMDA and kainate systems, while, based on less extensive evidence, decreasing the sensitivity of $GABA_B$ receptors in several brain regions, it seems reasonable to hypothesize that similar alterations in CCC-PPT may play a role in the disruption in W and REM sleep that are seen with chronic alcohol use and during withdrawal from alcohol. This hypothesis can be tested by both examining molecular evidence of alcohol-induced changes in receptor subunit expression within the CCC-PPT and evaluating alterations in sensitivity to the effects of $GABA_B$ and excitatory glutamate receptor agonists on W and REM sleep that result from chronic exposure to ethanol.

Acknowledgments

This work was supported by the National Institute of Health (USA) research grant numbers MH 59839 (to S.D.) and AA15923 (to D.A.C.).

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). fifth ed Washington, DC: American Psychiatric Publishing; 2013.
[2] National Institute on Alcohol Abuse and Alcoholism (⟨www.niaaa.nih.gov⟩). Alcohol facts and statistics (2014).
[3] Brower KJ. Alcohol's effects on sleep in alcoholics. Alcohol Res Health 2001;25:110–25.
[4] Landolt HP, Gillin JC. Sleep abnormalities during abstinence in alcohol-dependent patients. Aetiology and management. CNS Drugs 2001;15:413–25.
[5] Roehrs T, Roth T. Sleep, sleepiness, and alcohol use. Alcohol Res Health 2001;25:101–9.
[6] Roehrs T, Roth T. Sleep, sleepiness, sleep disorders and alcohol use and abuse. Sleep Med Rev 2001;5:287–97.
[7] Koob GF. A role for brain stress systems in addiction. Neuron 2008;59:11–34.
[8] Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology 2010;35:217–38.
[9] Koob GF. Theoretical frameworks and mechanistic aspects of alcohol addiction: alcohol addiction as a reward deficit disorder. Curr Top Behav Neurosci 2011;13:3–30.
[10] Ross S, Peselow E. The neurobiology of addictive disorders. Clin Neuropharmacol 2009;32:269–76.
[11] Valenzuela CF, Harris RA. Alcohol: neurobiology. In: Substance abuse: a comprehensive textbook. third ed Philadelphia, USA: Williams and Wilkins; 1997.
[12] Datta S, Maclean RR. Neurobiological mechanisms for the regulation of mammalian sleep–wake behavior: reinterpretation of historical evidence and inclusion of contemporary cellular and molecular evidence. Neurosci Biobehav Rev 2007;31:775–824.
[13] Datta S. Cellular and chemical neuroscience of mammalian sleep. Sleep Med 2010;11:431–40.
[14] Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. Nat Rev Neurosci 2002;3:591–605.
[15] Datta S. Sleep: learning and memory. In: Koob G, Le Moal M, Thompson R, editors. Encyclopedia of behavioral neuroscience. Oxford: Academic Press; 2010. p. 218–26.
[16] Dijk DJBD, Aeschbach D, Tobler I, Borbely AA. The effects of ethanol on human sleep EEG power spectra differ from those of benzodiazepine receptor agonists. Neuropsychopharmacology 1992;7:225–32.
[17] Gresham SC, Webb WB, Williams RL. Alcohol and caffeine: effect on inferred visual dreaming. Science 1963;140:1226–7.
[18] MacLean AW, Cairns J. Dose–response effects of ethanol on the sleep of young men. J Stud Alcohol 1982;43:434–44.
[19] Roehrs T, Papineau K, Rosenthal L, Roth T. Ethanol as a hypnotic in insomniacs: self administration and effects on sleep and mood. Neuropsychopharmacology 1999;20:279–86.
[20] Rundell OH, Lester BK, Griffiths WJ, Williams HL. Alcohol and sleep in young adults. Psychopharmacologia 1972;26:201–18.
[21] Stone BM. Sleep and low doses of alcohol. Electroencephalogr Clin Neurophysiol 1980;48:706–9.
[22] Williams DL, MacLean AW, Cairns J. Dose–response effects of ethanol on the sleep of young women. J Stud Alcohol 1983;44:515–23.
[23] Yules RB, Freedman DX, Chandler KA. The effect of ethyl alcohol on man's electroencephalographic sleep cycle. Electroencephalogr Clin Neurophysiol 1966;20:109–11.
[24] Landolt HP, Roth C, Dijk DJ, Borbely AA. Late-afternoon ethanol intake affects nocturnal sleep and the sleep EEG in middle-aged men. J Clin Psychopharmacol 1996;16:428–36.
[25] Ghosh TK, Copeland Jr RL, Alex PK, Pradhan SN. Behavioral effects of ethanol inhalation in rats. Pharmacol Biochem Behav 1991;38:699–704.
[26] Ghosh TK, Copeland Jr RL, Pradhan SN. Effects of ethanol inhalation on EEG in rats. Pharmacol Biochem Behav 1991;38:293–7.

[27] Hattan DG, Eacho PI. Relationship of ethanol blood level to REM and non-REM sleep time and distribution in the rat. Life Sci 1978;22:839–46.
[28] Hill SY, Reyes RB. Effects of chronic and acute ethanol administration on sleep in laboratory rats. J Stud Alcohol 1978;39:47–55.
[29] Kubota T, De A, Brown RA, Simasko SM, Krueger JM. Diurnal effects of acute and chronic administration of ethanol on sleep in rats. Alcohol Clin Exp Res 2002;26:1153–61.
[30] Mendelson WB, Hill SY. Effects of the acute administration of ethanol on the sleep of the rat: a dose–response study. Pharmacol Biochem Behav 1978;8:723–6.
[31] Gross MM, Goodenough DR, Hastey J, Lewis E. Experimental study of sleep in chronic alcoholics before, during, and after four days of heavy drinking with a nondrinking comparison. Ann N Y Acad Sci 1973;215:254–65.
[32] Gross MM, Hastey JM. The relation between baseline slow wave sleep and the slow wave sleep response to alcohol in alcoholics. Adv Exp Med Biol 1975;59:467–75.
[33] Wagman AM, Allen RP. Effects of alcohol ingestion and abstinence on slow wave sleep of alcoholics. Adv Exp Med Biol 1975;59:453–66.
[34] Prinz PN, Roehrs TA, Vitaliano PP, Linnoila M, Weitzman ED. Effect of alcohol on sleep and nighttime plasma growth hormone and cortisol concentrations. J Clin Endocrinol Metab 1980;51:759–64.
[35] Mello NK, Mendelson JH. Behavioral studies of sleep patterns in alcoholics during intoxication and withdrawal. J Pharmacol Exp Ther 1970;175:94–112.
[36] Mukherjee S, Kazerooni M, Simasko SM. Dose–response study of chronic alcohol induced changes in sleep patterns in rats. Brain Res 2008;1208:120–7.
[37] Mukherjee S, Simasko SM. Chronic alcohol treatment in rats alters sleep by fragmenting periods of vigilance cycling in the light period with extended wakenings. Behav Brain Res 2009;198:113–24.
[38] Sharma R, Engemann SC, Sahota P, Thakkar MM. Effects of ethanol on extracellular levels of adenosine in the basal forebrain: an in vivo microdialysis study in freely behaving rats. Alcohol Clin Exp Res 2010;34:813–8.
[39] Adamson J, Burdick JA. Sleep of dry alcoholics. Arch Gen Psychiatry 1973;28:146–9.
[40] Brower KJ, Aldrich MS, Hall JM. Polysomnographic and subjective sleep predictors of alcoholic relapse. Alcohol Clin Exp Res 1998;22:1864–71.
[41] Brower KJ, Aldrich MS, Robinson EA, Zucker RA, Greden JF. Insomnia, self-medication, and relapse to alcoholism. Am J Psychiatry 2001;158:399–404.
[42] De Soto CB, O'Donnell WE, Allred LJ, Lopes CE. Symptomatology in alcoholics at various stages of abstinence. Alcohol Clin Exp Res 1985;9:505–12.
[43] Drummond SP, Gillin JC, Smith TL, DeModena A. The sleep of abstinent pure primary alcoholic patients: natural course and relationship to relapse. Alcohol Clin Exp Res 1998;22:1796–802.
[44] Foster JH, Marshall EJ, Peters TJ. Application of a quality of life measure, the life situation survey (LSS), to alcohol-dependent subjects in relapse and remission. Alcohol Clin Exp Res 2000;24:1687–92.
[45] Gross MM. Sleep disturbances in alcoholism. In: Alcoholism: interdisciplinary approaches to an enduring problem. Munich, Germany: Addison-Wesley Publishing Co.; 1976. p. 257–309.
[46] Imatoh N, Nakazawa Y, Ohshima H, Ishibashi M, Yokoyama T. Circadian rhythm of REM sleep of chronic alcoholics during alcohol withdrawal. Drug Alcohol Depend 1986;18:77–85.
[47] Ishibashi M, Nakazawa Y, Yokoyama T, Koga Y, Miyahara Y, Hayashida N, et al. Cerebral atrophy and slow wave sleep of abstinent chronic alcoholics. Drug Alcohol Depend 1987;19:325–32.
[48] Williams HL, Rundell Jr OH. Altered sleep physiology in chronic alcoholics: reversal with abstinence. Alcohol Clin Exp Res 1981;5:318–25.
[49] Aubin HJ, Monfort JC, Benoit O, Goldenberg F, Roullet-Volmi MC, Barrucand D. Alcohol, sleep and biological rhythms. Neurophysiol Clin 1993;23:61–70.
[50] Brower KJ, Hall JM. Effects of age and alcoholism on sleep: a controlled study. J Stud Alcohol 2001;62:335–43.
[51] Gann H, Feige B, Hohagen F, van Calker D, Geiss D, Dieter R. Sleep and the cholinergic rapid eye movement sleep induction test in patients with primary alcohol dependence. Biol Psychiatry 2001;50:383–90.
[52] Gillin JC, Smith TL, Irwin M, Kripke DF, Schuckit M. EEG sleep studies in pure primary alcoholism during subacute withdrawal: relationships to normal controls, age, and other clinical variables. Biol Psychiatry 1990;27:477–88.
[53] Gillin JC, Smith TL, Irwin M, Butters N, Demodena A, Schuckit M. Increased pressure for rapid eye movement sleep at time of hospital admission predicts relapse in nondepressed patients with primary alcoholism at 3-month follow-up. Arch Gen Psychiatry 1994;51:189–97.
[54] Snyder S, Karacan I. Sleep patterns of sober chronic alcoholics. Neuropsychobiology 1985;13:97–100.
[55] Zarcone V. Alcoholism and sleep. Adv Biosci 1978;21:29–38.
[56] Gann H, Feige B, Fasihi S, van Calker D, Voderholzer U, Riemann D. Periodic limb movements during sleep in alcohol dependent patients. Eur Arch Psychiatry Clin Neurosci 2002;252:124–9.
[57] Landolt HP, Borbely AA. Alcohol and sleep disorders. Ther Umsch 2000;57:241–5.
[58] Brower KJ. Insomnia, alcoholism and relapse. Sleep Med Rev 2003;7:523–39.
[59] Clark CP, Gillin JC, Golshan S, Demodena A, Smith TL, Danowski S, et al. Increased REM sleep density at admission predicts relapse by three months in primary alcoholics with a lifetime diagnosis of secondary depression. Biol Psychiatry 1998;43:601–7.
[60] Mackenzie A, Funderburk FR, Allen RP. Sleep, anxiety, and depression in abstinent and drinking alcoholics. Subst Use Misuse 1999;34:347–61.
[61] Ehlers CL, Slawecki CJ. Effects of chronic ethanol exposure on sleep in rats. Alcohol 2000;20:173–9.
[62] Gitlow SE, Bentkover SH, Dziedzic SW, Khazan N. Persistence of abnormal REM sleep response to ethanol as a result of previous ethanol ingestion. Psychopharmacologia 1973;33:135–40.
[63] Mendelson WB, Majchrowicz E, Mirmirani N, Dawson S, Gillin JC, Wyatt RJ. Sleep during chronic ethanol administration and withdrawal in rats. J Stud Alcohol 1978;39:1213–23.
[64] Rouhani S, Dall'Ava-Santucci J, Bajenaru O, Emmanouilidis E, Tran G, Manicom R, et al. Effects of muscimol or homotaurine on sleep–wake states in alcohol-dependent rats during withdrawal. Pharmacol Biochem Behav 1998;59:955–60.
[65] Veatch LM. Disruptions in sleep time and sleep architecture in a mouse model of repeated ethanol withdrawal. Alcohol Clin Exp Res 2006;30:1214–22.
[66] Davis PA, Gibbs FA, Davis H, Jetter WW, Trowbridge LS. The effects of alcohol upon the electroencephalogram (brain waves). Q J Study Alcohol 1941;1:626–37.
[67] Engel GL, Rosenbaum M. Delerium III. Electroencephalographic changes associated with acute alcoholic intoxication. Arch Neurol Psychiatry 1945;53:44–50.
[68] Holmberg G, Martens S. Electroencephalographic changes in man correlated with blood alcohol concentration and some other conditions following standardized ingestion of alcohol. Q J Stud Alcohol 1955;16:411–24.
[69] Lehtinen I, Lang AH, Jantii V, Pakkanen A, Keskinen E, Nyrke T, et al. Ethanol-induced disturbance in human arousal mechanism. Psychopharmacology 1981;73:223–9.
[70] Lukas SE, Mendelson JH, Benedikt RA, Jones B. EEG alpha activity increases during transient episodes of ethanol-induced euphoria. Pharmacol Biochem Behav 1986;25:889–95.
[71] Michel CH, Batting K. Separate and combined psychophysiological effects of cigarette smoking and alcohol consumption. Psychopharmacology 1989;97:65–73.
[72] Cohen HL, Porjesz B, Begleiter H. Ethanol-induced alterations in electroencephalographic activity in adult males. Neuropsychopharmacology 1993;8:365–70.
[73] Ehlers CL, Wall TL, Schuckit MA. EEG spectral characteristics following ethanol administration in young men. EEG Clin Neurophysiol 1989;73:179–87.
[74] Newman HW. The effects of alcohol on the electroencephalogram. Stanford Med Bull 1959;17:55–60.
[75] Little HJ. The contribution of electrophysiology to knowledge of the acute and chronic effects of ethanol. Pharmacol Ther 1999;84:333–53.
[76] Murphree HB, Schultz RE, Jusko AG. Effects of high congener intake by human subjects on the EEG. Q J Stud Alcohol 1970;5(Suppl):50–61.
[77] Lehtinen I, Lang AH, Keskinen E. Acute effects of small doses of alcohol on the NSD parameters (normalized slope descriptors) of human EEG. Psychopharmacology 1978;60:87–92.
[78] Ehlers CL, Schuckit MA. EEG response to ethanol in sons of alcoholics. Psychopharmacol Bull 1988;24:434–7.
[79] Ehlers CL, Schuckit MA. EEG fast frequency activity in the sons of alcoholics. Biol Psychiatry 1990;27:631–41.
[80] Lukas SE, Mendelson JH, Woods BT, Mello NK, Teoh SK. Topographic distribution of EEG alpha activity during ethanol-induced intoxication in women. J Stud Alcohol 1989;50:176–85.
[81] Ehlers CL, Schuckit MA. Evaluation of EEG alpha activity in sons of alcoholics. Neuropsychopharmacology 1991;4:199–205.
[82] Bauer LO, Hesselbrock VM. EEG and subjective correlates of the risk for alcoholism. J Stud Alcohol 1993;54:577–89.
[83] Courtney KE, Polich J. Binge drinking effects on EEG in young adult humans. Int J Environ Res Public Health 2010;7:2325–36.
[84] Morzorati S, Lamishaw B, Lumeng L, Li TK, Bemis K, Clemens J. Effect of low dose ethanol on the EEG of ethanol preferring and non-preferring rats. Brain Res Bull 1988;21:101–4.
[85] Robeldo P, Lumeng L, Li TK, Ehlers CL. Effects of MK801 and diazepam on the EEG of P and NP rats. Alcohol Clin Exp Res 1994;18:363–8.
[86] Slawecki CJ, Bentancourt M, Li TK, Ehlers CL. Neurophysiological findings and drinking levels in high-alcohol-drinking (HAD) and low-alcohol-drinking (LAD) rats. Alcohol Clin Exp Res 2000;24:1492–9.
[87] Bauer LO. Electroencephalographic and autonomic predictors of relapse in alcohol-dependent patients. Alcohol Clin Exp Res 1994;18:755–60.
[88] Costa L, Bauer L. Quantitative electroencephalographic differences associated with alcohol, cocaine, heroin and dual-substance dependence. Drug Alcohol Depend 1997;46:87–93.
[89] Winterer GA, Kloppel B, Heinz A, Ziller M, Dufeu P, Schmidt LG, et al. Quantitative E.E.G. (QEEG) predicts relapse in patients with chronic alcoholism and points to a frontally pronounced cerebral disturbance. Psychiatry Res 1998;78:101–13.
[90] Finn PR, Justus A. Reduced EEG alpha power in the male and female offspring of alcoholics. Alcohol Clin Exp Res 1999;23:256–62.
[91] Rangaswamy M, Porjesz B, Chorlian DB, Wang K, Jones K, Bauer LO, et al. Beta power in the EEG of alcoholics. Biol Psychiatry 2002;52:831–42.
[92] Porjesz B, Begleiter H. Alcoholism and human electrophysiology. Alcohol Res Health 2003;27:153–60.
[93] Coutin-Churchman P, Moreno R, Anez Y, Vergara F. Clinical correlates of quantitative EEG alterations in alcoholic patients. Clin Neurophysiol 2006;117:740–51.

[94] Propping P, Kruger J, Mark N. Genetic disposition to alcoholism: An EEG study in alcoholics and their relatives. Hum Genet 1981;59:51–9.
[95] Bauer LO. Predicting relapse to alcohol and drug abuse via quantitative electroencephalography. Neuropsychopharmacology 2001;25:332–40.
[96] Coutin-Churchman P, Anez Y, Uzcategui M, Alvarez L, Vergara F, Mendez L, et al. Quantitative spectral analysis of EEG in psychiatry revisited: drawing signs out of numbers in a clinical setting. Clin Neurophysiol 2003;114:2294–306.
[97] Rangaswamy M, Porjesz B, Chorlian DB, Choi K, Jones KA, Wang K, et al. Theta power in the EEG of alcoholics. Alcohol Clin Exp Res 2003;27:607–15.
[98] Saleut-Zyhlarz GM, Arnold O, Anderer P, Oberndorfer S, Walter H, Lesch OM, et al. Differences in brain function between relapsing and abstaining alcohol-dependent patients, evaluated by EEG mapping. Alcohol Alcohol 2004;39:233–40.
[99] Jaaskelainen IP, Hirvonen J, Saher M, Pekkonen E, Sillanaukee P, Naatanen R, et al. Dose-dependent suppression by ethanol of transient auditory 40-Hz response. Psychopharmacology 2000;148:132–5.
[100] Campbell AE, Sumner P, Singh KD, Muthukumaraswamy SD. Acute effects of alcohol on stimulus-induced gamma oscillations in human primary visual and motor cortices. Neuropsychopharmacology 2014, http://dx.doi.org/10.1038/npp.2014.58 (PMID: 24622470).
[101] Padmanabhapillai A, Tang Y, Ranganathan M, Rangaswamy M, Jones KA, Chorlian DB, et al. Evoked gamma band response in male adolescent subjects at high risk for alcoholism during a visual oddball task. Int J Psychophysiol 2006;62:262–71.
[102] De Bruin EA, Biji S, Stam CJ, Bocker KBE, Kenemans JL, Verbaten MN. Abnormal EEG synchronization in heavily drinking students. Clin Neurophysiol 2004;115:2048–55.
[103] Coullaut-Valera R, Arbaiza I, Bajo R, Arrue R, Lopez ME, Coullaut-Valera J, et al. Drug polyconsumption is associated with increased synchronization of brain electrical-activity at rest and in a counting task. Int J Neural Syst 2014;24:1450005, http://dx.doi.org/10.1142/S0129065714500051.
[104] Sharma R, Engemann S, Sahota P, Thakkar MM. Role of adenosine and wake-promoting basal forebrain in insomnia and associated sleep disruptions caused by ethanol dependence. J Neurochem 2010;115:782–94.
[105] Thakkar MM, Engemann SC, Sharma R, Sahota P. Role of wake-promoting basal forebrain and adenosinergic mechanisms in sleep-promoting effects of ethanol. Alcohol Clin Exp Res 2010;34:997–1005.
[106] Thakkar MM, Engemann SC, Sharma R, Mohan RR, Sahota P. Sleep–wakefulness in alcohol preferring and non-preferring rats following binge alcohol administration. Neuroscience 2010;170:22–7.
[107] Majchrowicz E. Induction of physical dependence upon ethanol and the associated behavioral changes in rats. Psychopharmacologia 1975;43:245–54.
[108] Braconi S, Sidhpura N, Aujla H, Martin-Fardon R, Weiss F, Ciccocioppo R. Revisiting intragastric ethanol intubation as a dependence induction method for studies of ethanol reward and motivation in rats. Alcohol Clin Exp Res 2010;34:538–44.
[109] Majchrowicz E, Hunt WA. Temporal relationship of the induction of tolerance and physical dependence after continuous intoxication with maximum tolerable doses of ethanol in rats. Psychopharmacology 1976;50:107–12.
[110] Meert TF, Huysmans H. Repeated characterization of alcohol withdrawal reactions in rats chronically exposed to an alcohol liquid diet. Prog Neuropsychopharmacol Biol Psychiatry 1994;18:947–60.
[111] Macey DJ, Schulteis G, Heinrichs SC, Koob GF. Time-dependent quantifiable withdrawal from ethanol in the rat: effect of method of dependence induction. Alcohol 1996;13:163–70.
[112] Chung CS, Wang J, Wehman M, Rhoads DE. Severity of alcohol withdrawal symptoms depends on developmental stage of Long-Evans rats. Pharmacol Biochem Behav 2008;89:137–44.
[113] Serrano A, Rivera P, Pavon FJ, Decara J, Suarez J, Rodriguez de Fonseca F, et al. Differential effects of single versus repeated alcohol withdrawal on the expression of endocannabinoid system-related genes in the rat amygdala. Alcohol Clin Exp Res 2012;36:984–94.
[114] Gilpin NW, Smith AD, Cole M, Weiss F, Koob GF, Richardson HN. Operant behavior and alcohol levels in blood and brain of alcohol-dependent rats. Alcohol Clin Exp Res 2009;33:2113–23.
[115] Ruwe WD, Bauce L, Flemons WW, Veale WL, Pittman QJ. Alcohol dependence and withdrawal in the rat. An effective means of induction and assessment. J Pharmacol Methods 1986;15:225–34.
[116] Veatch LM. Disruptions in sleep time and sleep architecture in a mouse model of repeated ethanol withdrawal. Alcohol Clin Exp Res 2006;30:1214–22.
[117] Wiggins WF, Graef JD, Huitt TW, Godwin DW. Ethosuximide reduces ethanol withdrawal-mediated disruptions in sleep-related EEG patterns. Alcohol Clin Exp Res 2013;37:372–82.
[118] Fidler TL, Oberlin BG, Struthers AM, Cunningham CL. Schedule of passive ethanol exposure affects subsequent intragastric ethanol self-infusion. Alcohol Clin Exp Res 2009;33:1909–23.
[119] Simms JA, Steensland P, Medina B, Abernathy KE, Chandler LJ, Wise R, et al. Intermittent access to 20% ethanol induces high ethanol consumption in Long-Evans and Wistar rats. Alcohol Clin Exp Res 2008;32:1816–23.
[120] Kampov-Polevoy AB, Matthews DB, Gause L, Morrow AL, Overstreet DH. P rats develop physical dependence on alcohol via voluntary drinking: changes in seizure thresholds, anxiety, and patterns of alcohol drinking. Alcohol Clin Exp Res 2000;24:278–84.
[121] McCarley RW. Neurobiology of REM and NREM sleep. Sleep Med 2007;8:302–30.
[122] Davis KM, Wu JY. Role of glutamatergic and GABAergic systems in alcoholism. J Biomed Sci 2001;8:7–19.
[123] Gilpin NW, Koob GF. Neurobiology of alcohol dependence: focus on motivational mechanisms. Alcohol Res Health 2008;31:185–95.
[124] Harris RA. Ethanol actions on multiple ion channels: which are important. Alcohol Clin Exp Res 1999;23:1563–70.
[125] Harris RA, Mihic SJ. Alcohol and inhibitory receptors: unexpected specificity from a nonspecific drug. Proc Natl Acad Sci U S A 2004;101:2–3.
[126] Proctor WR, Diao L, Freund RK, Browning MD, Wu PH. Synaptic GABAergic and glutamatergic mechanisms underlying alcohol sensitivity in mouse hippocampal neurons. J Physiol 2006;575:145–59.
[127] Tsai G. Glutamatergic neurotransmission in alcoholism. J Biomed Sci 1998;5:309–20.
[128] Biggio G, Concas A, Follesa P, Sanna E, Serra M. Stress, ethanol, and neuroactive steroids. Pharmacol Ther 2007;116:140–71.
[129] Kelm MK, Criswell HE, Breese GR. Ethanol-enhanced GABA release: a focus on G protein-coupled receptors. Brain Res Rev 2011;65:113–23.
[130] Datta S, Patterson EH, Spoley EE. Excitation of the pedunculopontine tegmental NMDA receptors induces wakefulness and cortical activation in the rat. J Neurosci Res 2001;66:109–16.
[131] Datta S, Spoley EE, Patterson EH. Microinjection of glutamate into the pedunculopontine tegmentum induces REM sleep and wakefulness in the rat. Am J Physiol Regul Integr Comp Physiol 2001;280:R752–9.
[132] Datta S. Evidence that REM sleep is controlled by the activation of brain stem pedunculopontine tegmental kainate receptor. J Neurophysiol 2002;87:1790–8.
[133] Datta S, Spoley EE, Mavanji VK, Patterson EH. A novel role of pedunculopontine tegmental kainate receptors: a mechanism of rapid eye movement sleep generation in the rat. Neuroscience 2002;114:157–64.
[134] Datta S, Mavanji V, Patterson EH, Ulloor J. Regulation of rapid eye movement sleep in the freely moving rat: local microinjection of serotonin, norepinephrine, and adenosine into the brainstem. Sleep 2003;26:513–20.
[135] Datta S. Activation of pedunculopontine tegmental PKA prevents GABAB receptor activation-mediated rapid eye movement sleep suppression in the freely moving rat. J Neurophysiol 2007;97:3841–50.
[136] Datta S, Siwek DF, Stack EC. Identification of cholinergic and non-cholinergic neurons in the pons expressing phosphorylated cyclic adenosine monophosphate response element-binding protein as a function of rapid eye movement sleep. Neuroscience 2009;163:397–414.
[137] Datta S, Desarnaud F. Protein kinase A in the pedunculopontine tegmental nucleus of rat contributes to regulation of rapid eye movement sleep. J Neurosci 2010;30:12263–73.
[138] Ulloor J, Mavanji V, Saha S, Siwek DF, Datta S. Spontaneous REM sleep is modulated by the activation of the pedunculopontine tegmental GABAB receptors in the freely moving rat. J Neurophysiol 2004;91:1822–31.
[139] George O, Koob GF. Craving, context and the cortex. Nat Neurosci 2011;14:409–10.
[140] Nam HW, McIver SR, Hinton DJ, Thakkar MM, Sari Y, Parkinson FE, et al. Adenosine and glutamate signaling in neuron-glial interactions: implications in alcoholism and sleep disorders. Alcohol Clin Exp Res 2012;36:1117–25.
[141] Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. Neuron 2000;25:515–32.
[142] George O, Koob GF. Individual differences in prefrontal cortex function and the transition from drug use to drug dependence. Neurosci Biobehav Rev 2010;35:232–47.
[143] Gonzales RA, Job MO, Doyon WM. The role of mesolimbic dopamine in the development and maintenance of ethanol reinforcement. Pharmacol Ther 2004;103:121–46.
[144] Grace AA. The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving. Addiction 2000;95(Suppl 2):S119–28.
[145] Grant KA. The role of 5-HT3 receptors in drug dependence. Drug Alcohol Depend 1995;38:155–71.
[146] Myers RD, Veale WL. Alcohol preference in the rat: reduction following depletion of brain serotonin. Science 1968;160:1469–71.
[147] Siggins GR, Roberto M, Nie Z. The tipsy terminal: presynaptic effects of ethanol. Pharmacol Ther 2005;107:80–98.
[148] Smith RJ, Aston-Jones G. Noradrenergic transmission in the extended amygdala: role in increased drug-seeking and relapse during protracted drug abstinence. Brain Struct Funct 2008;213:43–61.
[149] Thorsell A, Neuropeptide Y. (NPY) in alcohol intake and dependence. Peptides 2007;28:480–3.
[150] Weiner JL, Valenzuela CF. Ethanol modulation of GABAergic transmission: the view from the slice. Pharmacol Ther 2006;111:533–54.
[151] Weiss F, Porrino LJ. Behavioral neurobiology of alcohol addiction: recent advances and challenges. J Neurosci 2002;22:3332–7.
[152] Woodward JJ. Ethanol and NMDA receptor signaling. Crit Rev Neurobiol 2000;14:69–89.
[153] Kumar S, Porcu P, Werner DF, Matthews DB, Diaz-Granados JL, Helfand RS, et al. The role of GABA(A) receptors in the acute and chronic effects of ethanol: a decade of progress. Psychopharmacology (Berl) 2009;205:529–64.

[154] Liang J, Suryanarayanan A, Abriam A, Snyder B, Olsen RW, Spigelman I. Mechanisms of reversible GABAA receptor plasticity after ethanol intoxication. J Neurosci 2007;27:12367–77.
[155] Lack AK, Christian DT, Diaz MR, McCool BA. Chronic ethanol and withdrawal effects on kainate receptor-mediated excitatory neurotransmission in the rat basolateral amygdala. Alcohol 2009;43:25–33.
[156] Peris J, Eppler B, Hu M, Walker DW, Hunter BE, Mason K, et al. Effects of chronic ethanol exposure on GABA receptors and GABAB receptor modulation of 3H-GABA release in the hippocampus. Alcohol Clin Exp Res 1997;21:1047–52.
[157] Boyd KN, Kumar S, O'Buckley TK, Morrow AL. Chronic ethanol exposure produces tolerance to elevations in neuroactive steroids: mechanisms and reversal by exogenous ACTH. J Neurochem 2010;115:142–52.
[158] Holmes A, Spanagel R, Krystal JH. Glutamatergic targets for new alcohol medications. Psychopharmacology (Berl) 2013;229:539–54.
[159] Datta S, Siwek DF. Single cell activity patterns of pedunculopontine tegmentum neurons across the sleep–wake cycle in the freely moving rats. J Neurosci Res 2002;70:611–21.
[160] Datta S, Siwek DF. Excitation of the brain stem pedunculopontine tegmentum cholinergic cells induces wakefulness and REM sleep. J Neurophysiol 1997;77:2975–88.
[161] Gann H, Feige B, Hohagen F, van Calker D, Geiss D, Dieter R. Sleep and the cholinergic rapid eye movement sleep induction test in patients with primary alcohol dependence. Biol Psychiatry 2001;50:383–90.
[162] Gillette MU, Abbott SM. Biological Timekeeping Sleep Med Clin 2009;4:99–110.
[163] Herzog ED. Neurons and networks in daily rhythms. Nat Rev Neurosci 2007;8:790–802.
[164] Hut RA, Van der Zee EA. The cholinergic system, circadian rhythmicity, and time memory. Behav Brain Res 2011;221:466–80.
[165] Mendoza J, Challet E. Brain clocks: from the suprachiasmatic nuclei to a cerebral network. Neuroscientist 2009;15:477–88.
[166] Moore RY. Organization and function of a central nervous system circadian oscillator: the suprachiasmatic hypothalamic nucleus. Fed Proc 1983;42:2783–9.
[167] Stephan FK, Zucker I. Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. Proc Natl Acad Sci U S A 1972;69:1583–6.
[168] Van Cauter E. Diurnal and ultradian rhythms in human endocrine function: a minireview. Horm Res 1990;34:45–53.
[169] Bina KG, Rusak B, Semba K. Localization of cholinergic neurons in the forebrain and brainstem that project to the suprachiasmatic nucleus of the hypothalamus in rat. J Comp Neurol 1993;335:295–307.
[170] Liu C, Ding JM, Faiman LE, Gillette MU. Coupling of muscarinic cholinergic receptors and cGMP in nocturnal regulation of the suprachiasmatic circadian clock. J Neurosci 1997;17:659–66.
[171] Jones BE. Arousal systems. Front Biosci 2003;8:s438–51.
[172] Jones BE. Activity, modulation and role of basal forebrain cholinergic neurons innervating the cerebral cortex. Prog Brain Res 2004;145:157–69.
[173] Anderson SM, Pierce RC. Cocaine-induced alterations in dopamine receptor signaling: implications for reinforcement and reinstatement. Pharmacol Ther 2005;106:389–403.
[174] Hashimoto JG, Forquer MR, Tanchuck MA, Finn DA, Wiren KM. Importance of genetic background for risk of relapse shown in altered prefrontal cortex gene expression during abstinence following chronic alcohol intoxication. Neuroscience 2011;173:57–75.
[175] Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. Neuron 2005;45:647–50.
[176] McFarland K, Lapish CC, Kalivas PW. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. J Neurosci 2003;23:3531–7.
[177] Park WK, Bari AA, Jey AR, Anderson SM, Spealman RD, Rowlett JK, et al. Cocaine administered into the medial prefrontal cortex reinstates cocaine-seeking behavior by increasing AMPA receptor-mediated glutamate transmission in the nucleus accumbens. J Neurosci 2002;22:2916–25.
[178] Schmidt HD, Anderson SM, Famous KR, Kumaresan V, Pierce RC. Anatomy and pharmacology of cocaine priming-induced reinstatement of drug seeking. Eur J Pharmacol 2005;526:65–76.
[179] Schmidt HD, Famous KR, Pierce RC. The limbic circuitry underlying cocaine seeking encompasses the PPTg/LDT. Eur J Neurosci 2009;30:1358–69.
[180] Mark GP, Shabani S, Dobbs LK, Hansen ST. Cholinergic modulation of mesolimbic dopamine function and reward. Physiol Behav 2011;104:76–81.
[181] Semba K, Fibiger HC. Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistochemical study. J Comp Neurol 1992;323:387–410.
[182] Sesack SR, Deutch AY, Roth RH, Bunney BS. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. J Comp Neurol 1989;290:213–42.
[183] Floresco SB, West AR, Ash B, Moore H, Grace AA. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat Neurosci 2003;6:968–73.
[184] Kelland MD, Freeman AS, Rubin J, Chiodo LA. Ascending afferent regulation of rat midbrain dopamine neurons. Brain Res Bull 1993;31:539–46.
[185] Lodge DJ, Grace AA. The laterodorsal tegmentum is essential for burst firing of ventral tegmental area dopamine neurons. Proc Natl Acad Sci U S A 2006;103:5167–72.
[186] Lodge DJ, Grace AA. The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. Neuropsychopharmacology 2006;31:1356–61.
[187] Charara A, Smith Y, Parent A. Glutamatergic inputs from the pedunculopontine nucleus to midbrain dopaminergic neurons in primates: Phaseolus vulgaris-leucoagglutinin anterograde labeling combined with postembedding glutamate and GABA immunohistochemistry. J Comp Neurol 1996;364:254–66.
[188] Cornwall J, Cooper JD, Phillipson OT. Afferent and efferent connections of the laterodorsal tegmental nucleus in the rat. Brain Res Bull 1990;25:271–84.
[189] Futami T, Takakusaki K, Kitai ST. Glutamatergic and cholinergic inputs from the pedunculopontine tegmental nucleus to dopamine neurons in the substantia nigra pars compacta. Neurosci Res 1995;21:331–42.
[190] Hallanger AE, Wainer BH. Ascending projections from the pedunculopontine tegmental nucleus and the adjacent mesopontine tegmentum in the rat. J Comp Neurol 1988;274:483–515.
[191] Oakman SA, Faris PL, Kerr PE, Cozzari C, Hartman BK. Distribution of pontomesencephalic cholinergic neurons projecting to substantia nigra differs significantly from those projecting to ventral tegmental area. J Neurosci 1995;15:5859–69.
[192] Oakman SA, Faris PL, Cozzari C, Hartman BK. Characterization of the extent of pontomesencephalic cholinergic neurons' projections to the thalamus: comparison with projections to midbrain dopaminergic groups. Neuroscience 1999;94:529–47.
[193] Omelchenko N, Sesack SR. Laterodorsal tegmental projections to identified cell populations in the rat ventral tegmental area. J Comp Neurol 2005;483:217–35.
[194] Steininger TL, Rye DB, Wainer BH. Afferent projections to the cholinergic pedunculopontine tegmental nucleus and adjacent midbrain extrapyramidal area in the albino rat. I. Retrograde tracing studies. J Comp Neurol 1992;321:515–43.
[195] Woolf NJ, Butcher LL. Cholinergic systems in the rat brain: IV. Descending projections of the pontomesencephalic tegmentum. Brain Res Bull 1989;23:519–40.
[196] Forster GL, Blaha CD. Pedunculopontine tegmental stimulation evokes striatal dopamine efflux by activation of acetylcholine and glutamate receptors in the midbrain and pons of the rat. Eur J Neurosci 2003;17:751–62.
[197] Klink R, de Kerchove d'Exaerde A, Zoli M, Changeux JP. Molecular and physiological diversity of nicotinic acetylcholine receptors in the midbrain dopaminergic nuclei. J Neurosci 2001;21:1452–63.
[198] Steidl S, Miller AD, Blaha CD, Yeomans JS. M(5) muscarinic receptors mediate striatal dopamine activation by ventral tegmental morphine and pedunculopontine stimulation in mice. PLoS One 2011;6:e27538.
[199] Kamens HM, Andersen J, Picciotto MR. The nicotinic acetylcholine receptor partial agonist varenicline increases the ataxic and sedative-hypnotic effects of acute ethanol administration in C57BL/6J mice. Alcohol Clin Exp Res 2010;34:2053–60.
[200] Kamens HM, Andersen J, Picciotto MR. Modulation of ethanol consumption by genetic and pharmacological manipulation of nicotinic acetylcholine receptors in mice. Psychopharmacology (Berl) 2010;208:613–26.
[201] McKee SA, Harrison EL, O'Malley SS, Krishnan-Sarin S, Shi J, Tetrault JM, et al. Varenicline reduces alcohol self-administration in heavy-drinking smokers. Biol Psychiatry 2009;66:185–90.
[202] Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, et al. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. J Addict Med 2013;7:277–86.
[203] Kranzler HR, Anton RF. Implications of recent neuropsychopharmacologic research for understanding the etiology and development of alcoholism. J Consult Clin Psychol 1994;62:1116–26.
[204] Pierucci-Lagha A, Feinn R, Modesto-Lowe V, Swift R, Nellissery M, Covault J, et al. Effects of rapid tryptophan depletion on mood and urge to drink in patients with co-morbid major depression and alcohol dependence. Psychopharmacology (Berl) 2004;171:340–8.
[205] Virkkunen M, Linnoila M. Serotonin in early onset, male alcoholics with violent behaviour. Ann Med 1990;22:327–31.
[206] Weiss F, Parsons LH, Schulteis G, Hyytia P, Lorang MT, Bloom FE, et al. Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. J Neurosci 1996;16:3474–85.
[207] Ting AKR, Dockstader C, Heinmiller A, Grieder T, van der Kooy D. GABA(A) receptors mediate the opposing roles of dopamine and the tegmental pedunculopontine nucleus in the motivational effects of ethanol. Eur J Neurosci 2009;29:1235–44.
[208] Fiorillo CDNW, Schultz W. The temporal precision of reward prediction in dopamine neurons. Nat Neurosci 2008;11:966–73.
[209] Totah NK, Kim Y, Moghaddam B. Distinct prestimulus and poststimulus activation of VTA neurons correlates with stimulus detection. J Neurophysiol 2013;110:75–85.
[210] Lammel S, Lim BK, Ran C, Huang KW, Betley MJ, Tye KM, et al. Input-specific control of reward and aversion in the ventral tegmental area. Nature 2012;491:212–7.

[211] Garcia-Rill E, Simon C, Smith K, Kezunovic N, Hyde J. The pedunculopontine tegmental nucleus: from basic neuroscience to neurosurgical applications. J Neural Transm 2011;118:1397–407.
[212] Garcia-Rill E, Kezunovic N, D'Onofrio S, Luster B, Hyde J, Bisagno V, et al. Gamma band activity in the RAS-intracellular mechanisms. Exp Brain Res 2014;232:1509–22.
[213] Simon C, Kezunovic N, Ye M, Hyde J, Hayar A, Williams DK, Garcia-Rill E. Gamma band unit and population responses in the pedunculopontine nucleus. J Neurophysiology 2010;104:463–74.
[214] Kezunovic N, Urbano FJ, Simon C, Hyde J, Smith K, Garcia-Rill E. Mechanism behind gamma band activity in the pedunculopontine nucleus (PPN). Eur J Neurosci 2011;34:404–15.